Table of Contents:

8.0 GUIDANCE ON CONDUCT OF CLINICAL RESEARCH:

- 8.1 Subject Recruitment
- 8.2 Procedure for Enlisting a Subject in a Protocol
- 8.3 Confidentiality
- 8.4 Informed Consent Process
- 8.5 Inclusion/Exclusion
- 8.6 Completion and filing of Study Documents
- 8.7 Drug Accountability
- 8.8 Adverse Event Reporting
- 8.9 Subject Accrual
- 8.10 Subject Follow Up Procedures:
- 8.11 FDA Annual Reporting:
- 8.12 Annual reports for protocols involving RDRC approval

Appendices:

Appendix A Belmont Report
Appendix B Example of Subject Records
Appendix C Example of Investigator Records
Appendix D Example of Case Report Form Checklist.

Table of Acronyms:

AE - Adverse event
BNL - Brookhaven National Laboratory
CFR - Code of Federal Regulations
CRF - Case Report Form
CRA - Clinical Research Associate
CRC - BNL Clinical Research Center
DHHS - Department of Health and Human Services
DOE - Department of Energy
ESR - Experimental Safety Review
FDA - Food and Drug Administration
HHS - Health and Human Services
IND - Investigational New Drug
IRB - Institutional Review Board
NIDA - National Institute of Drug Abuse
NIH - National Institutes of Health
OPRR - Office for Protection Research Risk
ORA - BNL Office of Research Administration
PI - Principal Investigator
QA - Quality Assurance
QACSC - CRC Quality Assurance, Care and Safety Committee
RP - Responsible Physician
RDRC - Radioactive Drug Research Committee
SAE - Serious Adverse Event

INTRODUCTION`

The Brookhaven National Laboratory (BNL) operated by Brookhaven Science Associates (BSA) has an Multiple Project Assurance on file with the Office for Protection from Research Risks (OPRR; subdivision of the Department of Health and Human Services). This document provides written assurance that all research conducted at this institution that involves human subjects will be in compliance with the Federal Policy for the Protection of Human Subjects, specifically 45CFR46 and 21CFR50 and 21CFR56 (Federal Policy) and 10CFR745.

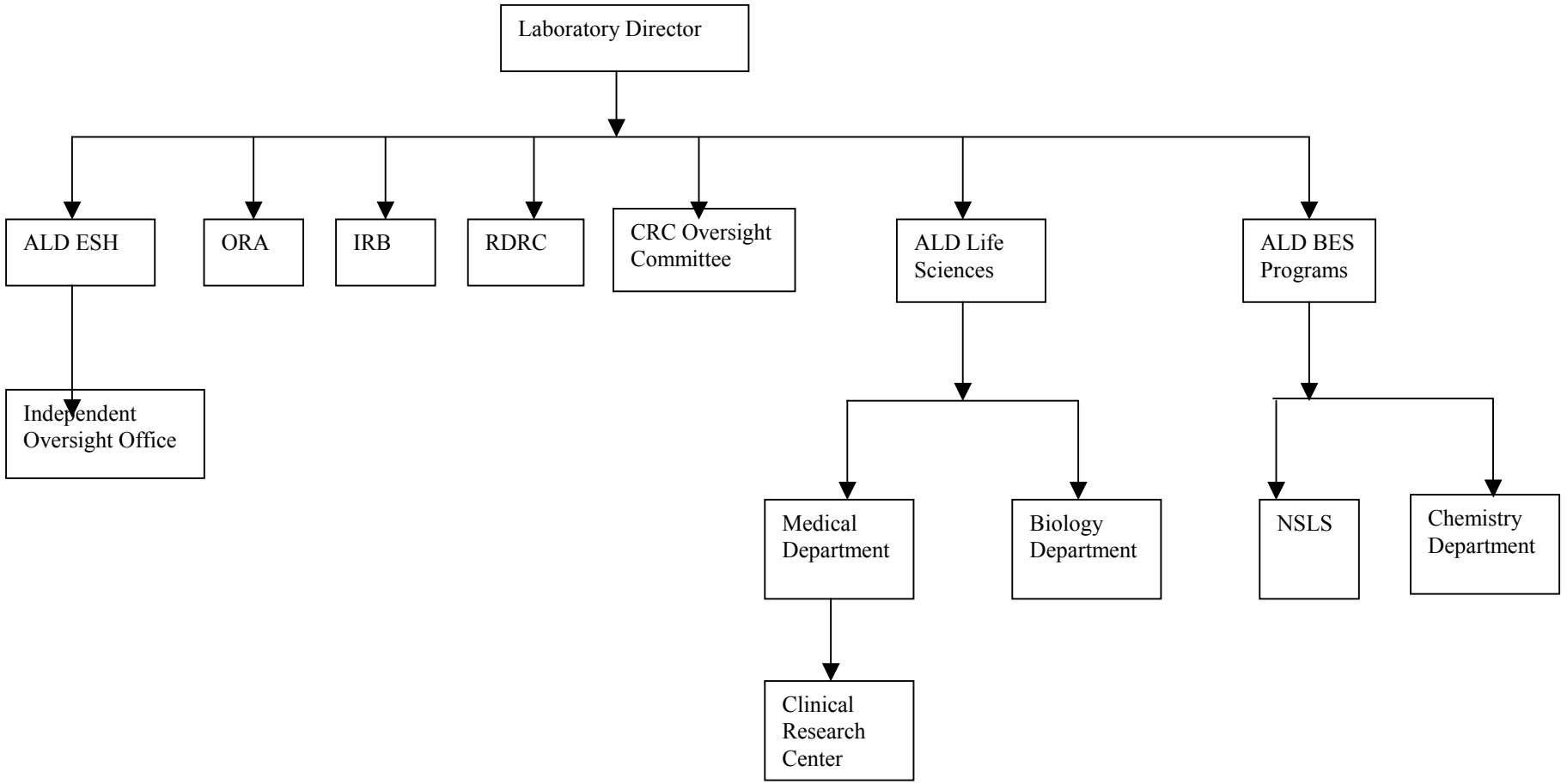
The basic ethical principles that underlie the Federal Policy are summarized in The Belmont Report. These regulations, specifically covering research from grants funded by the National Institutes of Health, have been adopted by Brookhaven National Laboratory to cover ALL research activities involving human subjects, regardless of source of funding.

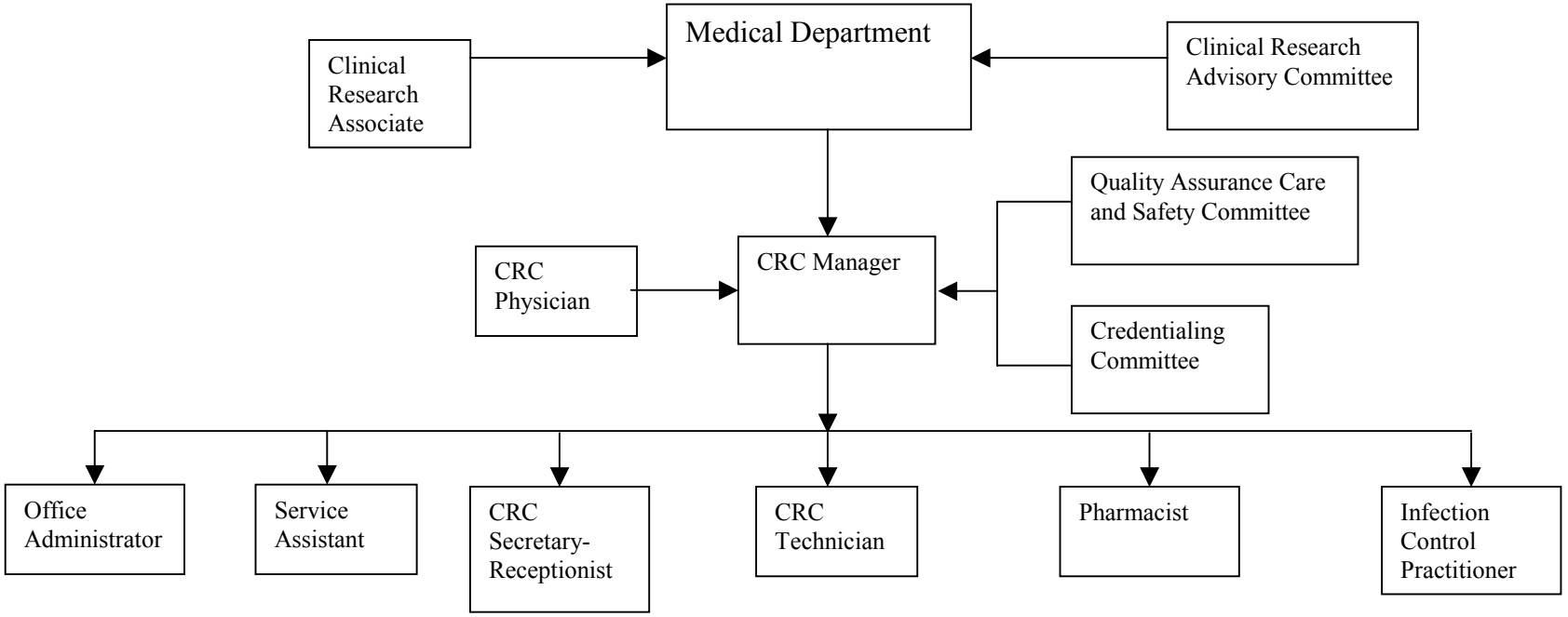
An organizational chart for the human studies research program at BNL is given on the following page.

The BNL Clinical Research Center (CRC) operates in compliance with Sections 3 and 5.11 of the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice.

The IRB reports to the Director of the Laboratory. The CRC reports to the Chairman of the Medical Department. The Office of Research Administration(ORA) serves as the liaison between the research investigators and IRB. The ORA provides administrative and secretarial support for the committee, and assists the investigators through the application and approval process. The ORA acts on behalf of the committee and Laboratory when providing assurance of human subjects approval to sponsoring agencies, or when dealing with regulatory agencies. The ORA is responsible for regularly monitoring the IRB's compliance, and updating procedures with current and/or new relevant federal or state regulations.

The Clinical Research Associate (CRA) will provide assistance to the investigators in the preparation of the documents necessary to carry out human research at BNL.


Laboratory Director
ALD ESH
ORA
IRB
RDRC
CRC Oversight Committee
ALD Life Sciences
ALD BES Programs
Independent Oversight Office
Medical Department
Biology Department
NSLS
Chemistry Department
Clinical Research Center


Medical Department
Clinical Research Associate
Clinical Research Advisory Committee
Quality Assurance Care and Safety Committee
CRC Physician
CRC Manager
Credentialing Committee
Office Administrator
Service Assistant
CRC Secretary-Receptionist
CRC Technician
Pharmacist
Infection Control Practitioner

1.0 INSTITUTIONAL COMMITMENT

BNL is committed to the policies and procedures established in this document. BNL relies heavily on the integrity of the clinical and professional staff to abide by the policies and procedures established in this document. Procedures to assure compliance include:

a. Failure by any staff member or collaborator to observe these policies and procedures will be considered serious misconduct subject to sanctions, including possible termination of appointment on the Clinical Research Center (CRC) Clinical Staff and /or BNL.

b. BNL has established the following procedure to report an incident.

Notice of incident:

Any person involved with a human study program at BNL who feels there has been or there is the potential for an adverse event, any injury or unanticipated problem involving risk to a subject or a noncompliance issue, is required to report it immediately to the Responsible Physician (RP) of the protocol. The Responsible Physician has the responsibility to evaluate the incident and report it, as appropriate, to the ORA using the Adverse Event Report form. (See CRC Policy 4.6, Adverse Event Reporting)

HUMAN SUBJECT RESEARCH DEFINED:

All research that involves human subjects must be reviewed by the Institutional Review Board (IRB) and the Department Chair. This includes a wide variety of activities, such as in vivo and in vitro studies, research using medical records, collection of data through surveys or observation, research using existing pathological specimens, discarded tissue or secretions, use of investigational drugs or devices and randomized trials. Refer also to 45 CFR 46

The following definitions, apply:

Research: Research is a systematic investigation designed to produce general knowledge. This may involve direct interactions or interventions (blood withdrawal, injection of compound, scanning, use of questionnaires, etc.), or indirect (analysis of specimens or data) interactions.

Human Subject: A human subject is a living individual about whom an investigator obtains either 1) data through intervention or interaction with the individual; or 2) identifiable, private information about an individual.

Minimal Risk: The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Sponsor-Investigator: The usual situation at BNL is that the Principal Investigator acts as both sponsor and investigator for a protocol. This implies that the PI must carry out all the responsibilities of both the sponsor and the investigator according to Federal Regulations. A Sponsor-Investigator is an individual who both initiates and conducts a clinical investigation and under whose immediate direction the investigational drug is being administered or dispensed.

2.0 FEDERAL REGULATIONS GOVERNING CLINICAL RESEARCH:

The following regulations and guidelines are concerned with human subject research and all individuals participating in clinical research should be familiar with their content :

1. Code of Federal Regulations (CFR) Title 10, Part 745 [Department of Energy Human Subjects regulations]

2. DOE Order 481.1 - Work for Others (Non-Department of Energy Funded Work)

3. DOE Order 1300.3 - Policy on the Protection of Human Subjects

4. Code of Federal Regulations (CFR) Title 45, Part 46 [Department of Health and Human Services (HHS) Human Subjects regulations]

5 Code of Federal Regulations (CFR) Title 21, Part 50 [Food and Drug Administration (FDA) Human Subjects regulations]

6. National Institute of Drug Abuse (NIDA) Guidelines for the Conduct of Substance Abuse Research

7. Controlled Substances Act of 1970, 21 CFR 1300-end

8. Code of Federal Regulations (CFR) Title 21, Part 361.1 [Radioactive Drugs for Certain Research Uses]

9. 21 CFR 812 (Investigational device exemptions)

10. International Conference on Harmonization (ICH) Guideline for Good Clinical Practice.

11. 21 CFR 312 (Investigational New Drugs)

12. 314 FDA (Applications for Approval to Market a New Drug)

3.0 SUMMARY OF THE BELMONT REPORT

In 1974, the passage of the National Research Act established the National Commission for the Protection of Human Subjects of biomedical and Behavioral Research. The Commission published the *Belmont Report* (see Appendix A) which articulates the basic ethical principles that guide the conduct of research with human subjects and forms the foundation of 45 CFR 46. Three principles were defined in the report as basic to the protection of human subjects: 1) respect, 2) beneficence, and 3) justice. All BNL human subjects research should be guided by the ethical principles set forth in the Belmont Report.

Respect for Persons: In consideration of respect for persons, investigators are required to seek voluntary informed consent from potential subjects. Voluntary informed consent means that subjects are given free choice to decide about participation, and the study is fully described in terms that are easy to understand. The consent form should include adequate information about the study risks and benefits that will assist subjects in deciding whether to participate in research. In addition, respect means honoring the privacy of individual and maintaining the confidentiality of data obtained. Respect for minors and individuals who are immature or incapacitated, perhaps even to the extent of excluding them from participation in certain research. The extent of protection depends upon the level of autonomy the person possesses.

Beneficence: The principle of beneficence requires that researchers maximize the potential benefits to the subjects and minimize the risks of harm. Benefits to the subjects, or generalizable knowledge gained from the research, should balance or outweigh the risks.

Justice: The principle of justice means that subjects are selected fairly and that the risks and benefits of research are distributed equitably. Investigators should take precautions not to select subjects simple because of the subjects' easy availability, their compromised position, or because of social, racial, gender, economic or cultural biases. Investigators should base inclusion criteria on those factors that most effectively and soundly address the research problem.

Research with vulnerable populations (mentally disabled, children) requires special justification. Equitable inclusion of both men and women of all ages and individuals from diverse racial/ethnic backgrounds is important to ensure that they receive an equal share of the benefits or research and that they do not bear a disproportionate share of its burdens. Participation should not be restricted without medical or scientific justification.

4.0 ORGANIZATIONS INVOLVED IN HUMAN SUBJECT RESEARCH AT BNL:

The organizational charts for the following organizations are shown on the next two pages (attachments 1 and 2)

4.1 Institutional Review Board

The Institutional Review Board (IRB) is established by BNL SPI 7-03 and authorized by a memo from the Laboratory Director. Its jurisdiction includes all research involving human subjects performed at or in conjunction with Brookhaven National Laboratory (BNL) and its employees, as defined by 10CFR 745, regardless of the Principal Investigator's (PI) appointment or relationship with BNL.

The IRB is guided by the principles set forth in the Laboratory's Multiple Project Assurance between Brookhaven Science Associates, LLC (BSA) and the Department of Health and Human Services (DHHS) which creates the Office of Human Subjects Research Administration (ORA).

4.1.1 Authority of the IRB

The IRB has the authority to approve, to require modification as a condition of approval, to require additional information prior to committee review, and to disapprove proposed research that are within its scope of authority as per the authorization memo from the Laboratory Director. The IRB has the authority to suspend, place restrictions or terminate any ongoing approved protocol. Furthermore, the IRB has the authority to determine whether or not any research activity is covered by these policies and procedures and whether it requires review by the IRB. A more complete description of IRB policies and procedures can in found at the ORA website.

4.1.2 Responsibility of the IRB:

The IRB has the responsibility to:

a) consider the following in their review of all ongoing and initial protocols:
   1) minimization of risk to research subjects;
   2) that risks are reasonable in relation to the potential benefit and the importance of knowledge that may be reasonably expected to result;
   3) the informed consent process to be employed;
   b) require progress reports from Principal Investigators ;
   c) oversee the conduct of the study;
   d) report to OPRR, FDA and the sponsor any unanticipated problem involving risk to a subject or any instance of serious, or continuing noncompliance with NIH and/or FDA regulations or any involuntary suspension/termination of a protocol.

4.2 Radioactive Drug Research Committee

SPI 7-03 also establishes the policy that any experimental radioactive drug used in human subject research meets the standards established by the Food and Drug Administration as authorized by paragraph 361.1 of 21 CFR 361.1. The Radioactive Drug Research Committee (RDRC) is responsible for such compliance.

The RDRC is authorized by the Food and Drug Administration (FDA) to approve human subjects research with radioactive drugs which are administered to human research subjects in a research project intended to obtain basic information regarding the metabolism of a radioactively labeled drug or research regarding human physiology, pathophysiology, or biochemistry. The RDRC shall not approve research of a radioactive drug intended for immediate therapeutic, diagnostic, or similar purposes, or research of a radioactive drug to determine the safety and effectiveness of the drug in humans.

All protocols which potentially involve human subjects and radioactive drugs must be reviewed by the RDRC prior to consideration by the IRB.

4.3 Office of Research Administration

The Office of Research Administration (ORA) has the responsibility to provide support for the Institutional Review Board (IRB) and the Radioactive Drug Research Committee (RDRC) for human subjects research.

4.4 Clinical Research Center

The Clinical Research Center (CRC) is empowered by the Director of BNL through the SPI 7-01. The CRC has the responsibility to provide clinical support and oversight for studies involving human subjects. The CRC has the responsibility to provide an environment in which human research studies can be conducted in a manner compliant with the federal guidelines in 10 CFR 745, 45 CFR 46 and commensurate with JCAHO standards. All personnel working with human subjects are required to have their credentials and training status reviewed and approved through the CRC prior to working with human subjects. Studies may not be initiated and will not be scheduled until the CRA approves investigator files and forms associated with a protocol. For more information about the CRC, please refer to the other sections of the CRC Policies and Procedures Manual.

5.0 INVESTIGATOR ROLES AND RESPONSIBILITIES:

These descriptions may be attached to the Investigator's existing R2A2

R2A2 Principal Investigator

Role: Propose, plan and execute scientific investigations involving human subjects in pursuit of scientific excellence.

Responsibilities

1. Know and adhere to rules and regulations governing research involving human subjects including the Belmont Report, NIDA Guidelines for the Conduct of Substance Abuse Research, Good Clinical Practice Guidelines, and NIH regulations.
2. Completed BNL annual training for conduct of human subjects research prior to start of protocol
3. Prepare initial clinical research protocol and any addendum thereto that defines a research program that justifies the use of human subjects and is compliant with regulatory requirements.
4. Identify in the protocol the appropriately credentialed Responsible Physician.
5. Submit the initial clinical research protocols and any modifications of the approved protocols to the IRB for approval prior to starting any work; retain copies of all correspondence with the ORA/IRB.
6. Submit substantive annual reports to the IRB including a presentation of research findings and accurate subject accrual information.
7. Ensure no deviations from the approved protocol occur by the research team conducting work under that protocol.
8. Ensure that the Responsible Physician or a Participating Physician under the protocol will be available on site during a subject study in accordance with the approved protocol.
9. Ensure that all personnel working on an approved protocol are appropriately credentialed, are appropriately qualified for their duties, and that their training is kept up to date (facility specific and human studies specific training).
10. Ensure that all personnel working on an approved protocol have access to and knowledge of the most current version of the approved protocol.
11. Report any unusual or adverse event, or unanticipated problem, to the ORA within 72 hours; report serious adverse events to the funding agency; in the case of death or major accident, the event must be reported in accordance with the CRC and BNL Reporting Policy
12. Prepare investigator records and subject records according to funding agency requirements and Good Clinical Practice Guidelines
13. Keep all human subject records confidential. Investigators are required to maintain and protect the privacy and confidentiality of all personally identifiable information on subjects, except as required by law or released with the written permission of the subject. Certificates

of Confidentiality should be applied for when data about sensitive information (illegal behavior, drug use, etc.) is collected about a human subject.

14. Ensure scheduling or registering of all subjects with the CRC
15. Perform duties as defined below for Participating Physician when protocol does not require that a physician be present during the study
16. Submit an annual report to the FDA for each IND on which the PI is the Sponsor/Investigator
17. Provide required information on radioactive drugs to the RDRC

Accountabilities:

1. To DOE and Laboratory Management for meeting scientific challenges and conduct innovative research
2. To the Department Chair and Laboratory Management for performance of the aforementioned tasks.
3. To human subjects for meeting the standards of Good Clinical Practices and for protecting their privacy and confidentiality

Authorities:

1. Sign off on experimental safety reviews and protocols.
2. Identify equipment and project needs.
3. Manage assigned resources to complete research.
4. Take required action to meet project quality, budget and schedule.
5. Take any actions deemed necessary to ensure the well-being of the human subjects

These descriptions may be attached to the Investigator's existing R2A2

R2A2 RESPONSIBLE PHYSICIAN/PARTICIPATING PHYSICIAN

(* denotes responsibilities that can only be carried out by Responsible Physician)

Role

Provide overall clinical care of human subjects enlisted in protocol in accordance with Good Clinical Practices.

Responsibilities

1. Know and adhere to rules and regulations governing research involving human subjects including the Belmont Report, NIDA Guidelines for the Conduct of Substance Abuse Research, Good Clinical Practice Guidelines, and NIH regulations.
2. Completed BNL annual training for conduct of human subjects research prior to start of protocol
3. Together with the PI develop all protocol specific forms and record format prior to implementation of approved protocol
4. *Ensure that all Subject Records for a particular protocol are in place and are consistent with the protocol
5. *Review Adverse Event Report for medical consequences
6. *Ensure that the facility is medically equipped to safely carry out the research protocol and that the Crash Cart (if required) is available and that the proper medications and equipment are present
7. Ensure that an adequate number of clinical staff are trained in Basic LS/CPR to provide coverage during clinical studies
8. Discharge of the subject after completion of the study
9. Ensure that the completed Subject Record is returned to the CRC upon completion of the study
10. Ensure that an individual is responsible for the inspection of the Crash Cart for the protocol before the first study of the day and that the staff are adequately trained to respond to an emergency using the Crash Cart
11. Ensure that the staff are using barrier protection devices and/or other procedures necessary to control infectious disease
12. Ensure that qualified staff members are available to perform required tasks for a scheduled study
13. Administer informed consent to subject and obtain appropriate documentation that consent process completed

Accountabilities

1. To the PI for ensuring clinical care for subjects in that protocol

2. To the Chair of Medical Department and Laboratory Management for ensuring the performance of the aforementioned tasks.

Authorities

1. Take actions deemed necessary for the well-being of the subjects in Human Studies.

6.0 HUMAN STUDIES RESEARCH SUBMISSION PROCESS

The flow charts for the submission of materials for human subjects research are given on the following pages.

6.1 Grant Preparation and Department Review

After the grant is written, it may be submitted to the department chair for review. The department chair will review the proposal for scientific merit and to ensure that department resources are sufficient to carry out the research. This review process will be department specific.

6.2 Preliminary IRB Grant Review

Grants being submitted to funding agencies which involve human subjects usually require IRB approval during the submission process . The grant application must be submitted to the ORA for transmittal to the IRB after the grant has received a score from the funding agency that makes the grant eligible for funding.

6.3 DOE Review (if Required)

The grant application may be submitted to the DOE area office for review.

6.4 Human Studies Protocol Categories for IRB Submission:

Once the funding for the project has been obtained, a protocol must be written for IRB and Department review. The protocol submission form and the definitions of types of protocols may be obtained from the ORA.

6.5 Protocol Application Submission Package:

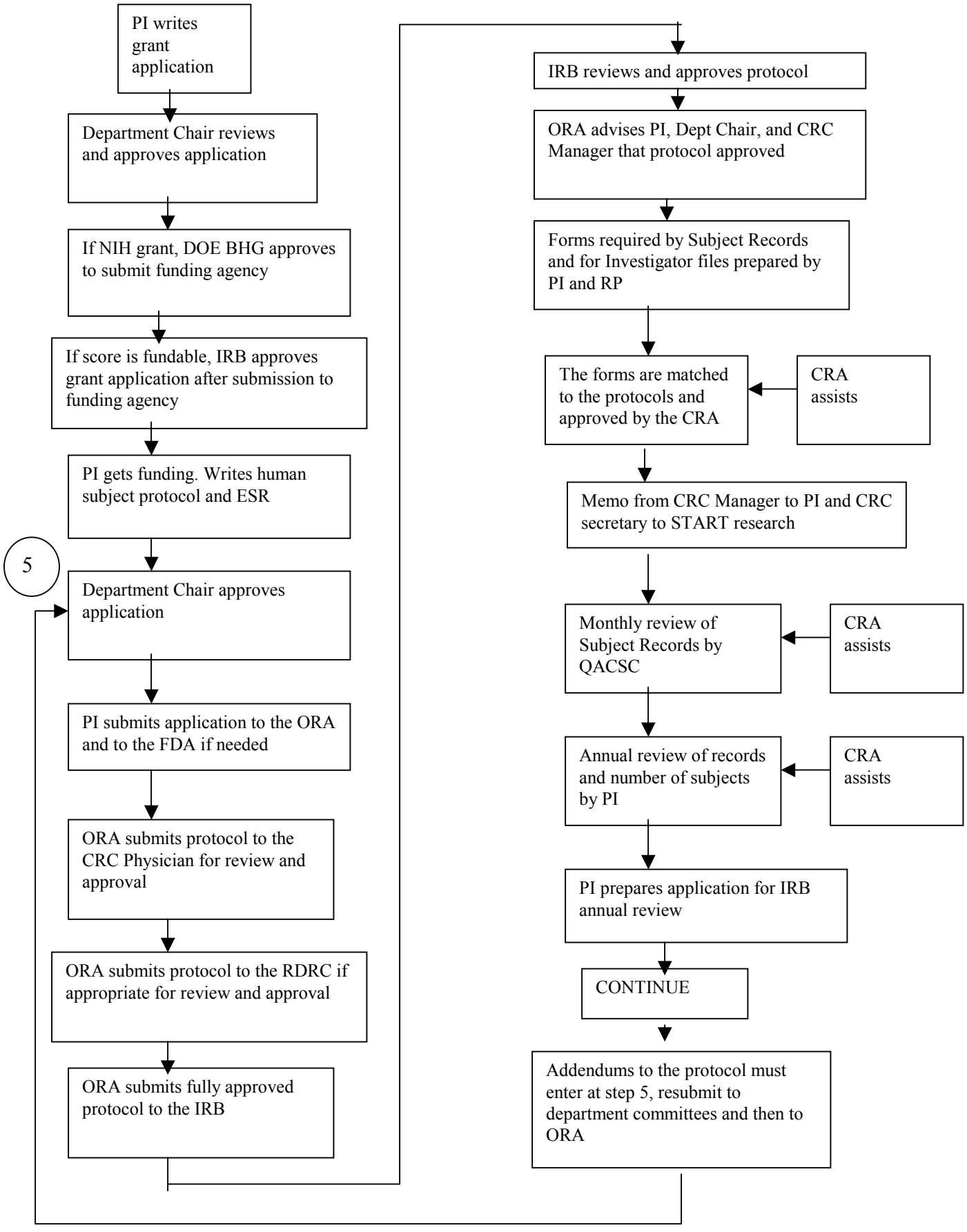
For a new protocol, the Principal Investigator is sent an Initial Application Package. Each new PI receives an IRB Investigator's Manual which contains the rules and regulations regarding human subject research, as well as pertinent IRB forms:

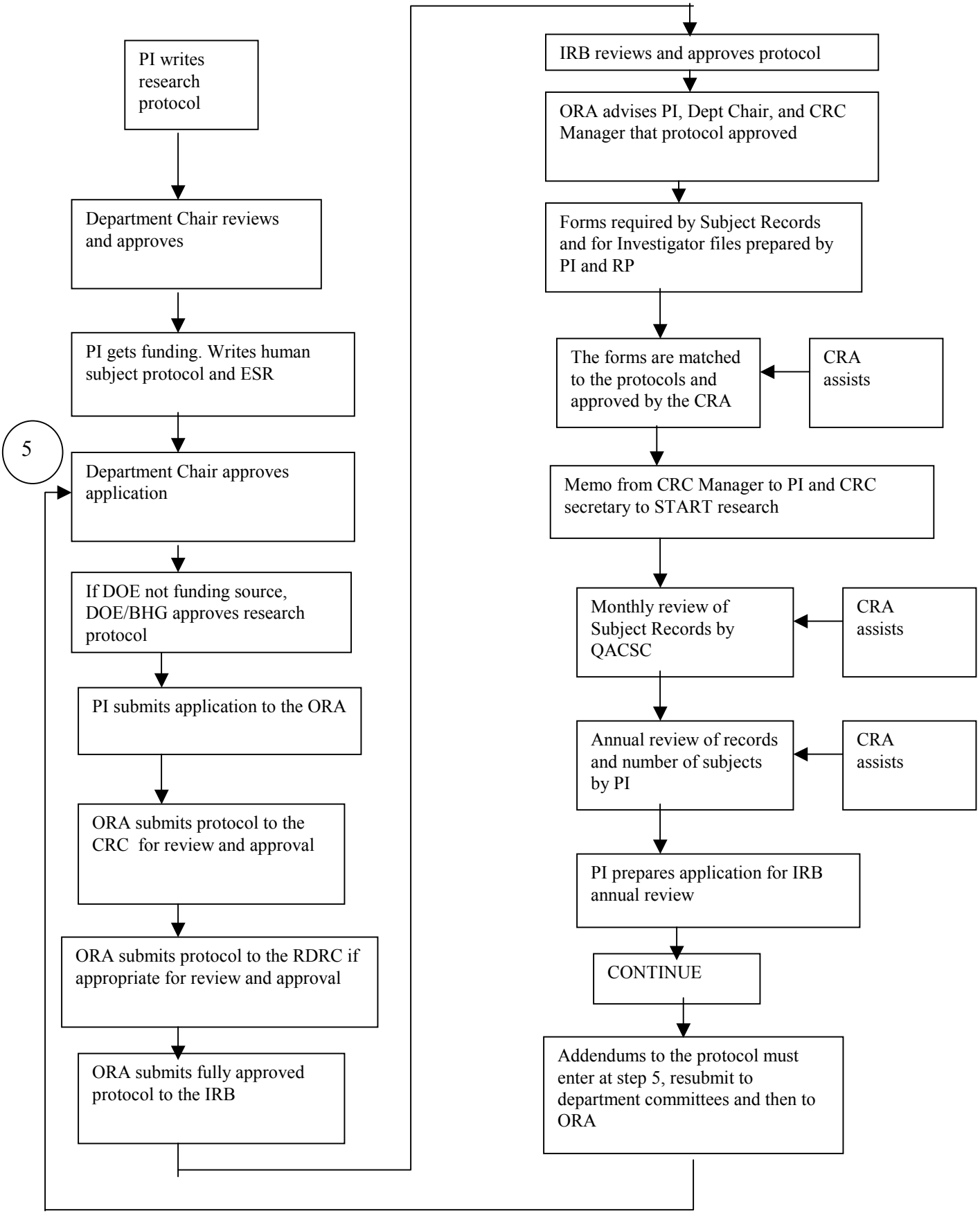
Documents and forms are available on the ORA web site at www.ora.bnl.gov.

For protocols involving investigational drugs, application to the FDA is also required. Information for submitting an application (Forms 1571/1572) can be obtained at http://www.fda.gov/cder/forms/1571-1572-help.html .

6.6 Protocol Review Process: Protocols are reviewed under the following review processes:

a) Preliminary ORA Review: This review determines if the protocol is under the jurisdiction of the human research regulations.
b) Department Review: The PI's Department Chair and quality assurance committee will review the protocol and the Department Chair will sign off prior to IRB review.


PI writes grant application
Department Chair reviews and approves application
If NIH grant, DOE BHG approves to submit funding agency
If score is fundable, IRB approves grant application after submission to funding agency
PI gets funding. Writes human subject protocol and ESR
5
Department Chair approves application
PI submits application to the ORA and to the FDA if needed
ORA submits protocol to the CRC Physician for review and approval
ORA submits protocol to the RDRC if appropriate for review and approval
ORA submits fully approved protocol to the IRB
IRB reviews and approves protocol
ORA advises PI, Dept Chair, and CRC Manager that protocol approved
Forms required by Subject Records and for Investigator files prepared by PI and RP
The forms are matched to the protocols and approved by the CRA
CRA assists
Memo from CRC Manager to PI and CRC secretary to START research
Monthly review of Subject Records by QACSC
CRA assists
Annual review of records and number of subjects by PI
CRA assists
PI prepares application for IRB annual review
CONTINUE
Addendums to the protocol must enter at step 5, resubmit to department committees and then to ORA


PI writes research protocol
Department Chair reviews and approves
PI gets funding. Writes human subject protocol and ESR
5
Department Chair approves application
If DOE not funding source, DOE/BHG approves research protocol
PI submits application to the ORA
ORA submits protocol to the CRC for review and approval
ORA submits protocol to the RDRC if appropriate for review and approval
ORA submits fully approved protocol to the IRB
IRB reviews and approves protocol
ORA advises PI, Dept Chair, and CRC Manager that protocol approved
Forms required by Subject Records and for Investigator files prepared by PI and RP
The forms are matched to the protocols and approved by the CRA
CRA assists
Memo from CRC Manager to PI and CRC secretary to START research
Monthly review of Subject Records by QACSC
CRA assists
Annual review of records and number of subjects by PI
CRA assists
PI prepares application for IRB annual review
CONTINUE
Addendums to the protocol must enter at step 5, resubmit to department committees and then to ORA

c) Radioactive Drug Research Committee Review: The RDRC will review the protocol if there is a radioactive drug involved which does not have an IND. The chair of the RDRC will sign off prior to IRB review.

d) IRB Review: If the protocol is determined by the ORA preliminary review to be a human study requiring full board approval, the protocol is forwarded to the IRB for an initial review.

e) CRA Review: After the protocol has received IRB approval, a review will be carried out by the CRA to ensure that all the forms and documentation are in order. This must be accomplished before research can be started.

f) Modification/Addendum Review: This review is required whenever a Principal Investigator changes an approved protocol for any reason, including an unanticipated reaction of a subject that requires a change in procedures. This addendum must be resubmitted to the Department for review.

g) Recertification Review: Each protocol must be recertified by the IRB at a minimum of once a year. At the time of an Initial or Modification/Addendum Review, the IRB will determine an appropriate certification period (no greater than one year) based on factors such as the type of subjects involved, including disease state and/or vulnerability, previously reported adverse events and investigator/group experience with the proposed work.

Protocol Reviews:
Any clinical protocol which involves BNL shall be reviewed and must be approved by the IRB prior to the beginning of research. All forms and procedures are contained in the IRB Investigator's Manual and are available from the ORA and the web site.

6.6.1 Preliminary ORA Review: All protocols or protocol modifications/addendums receive a Preliminary Review by the ORA, in consultation with the IRB Chairman, to determine the level of risk to the subject.

6.6.2 Departmental Review

The Principal Investigator must have their Department Chair approve the protocol. The Department Chair must consider the following during their review:

a) Appropriateness of conducting the proposed study at Brookhaven;
b) Source of funding for the project;
c) Safety issues, including potential personnel and subject hazards;
d) Expertise and experience of individuals listed as participating in the project;
e) Training status of individuals listed as participating in the project;
f) Availability of departmental resources for the proposed studies.

g) That the scientific processes (such as isotope preparation, machine calibration, tissue culture work, etc.) related to the protocol are adequately performed and controlled so as to support the risk factors listed by the Principal Investigator.

h) Ensure that Experimental Safety Reviews, Quality Assurance reviews, and training needs are met from their own department and from other participating departments for research projects where the PI is from the Chair's department, but which involve other departments.

All forms must be signed and dated by the Principal Investigator, Responsible Physician and Department Chair/Division Head. If the Principal Investigator, Responsible Physician and Department Chair/Division Head are the same person, an alternate Department Chair/division Head should review and sign the application to avoid a possible conflict of interest.

6.6.3 CRC Physician Review

The CRC Physician reviews the proposals to determine:

a) the adequacy and appropriateness of the staff assigned to the project

b) the adequacy and appropriateness of the facilities to ensure necessary subject care

c) to evaluate the medical risks associated with the proposed experiment.

6.6.4 Radioactive Drug Research Committee Review

If a radioactive drug is to be used for which no Investigational New Drug (IND) application has been submitted, RDRC review and approval is necessary before research can begin. IRB review and approval is also necessary if the work is to be done in human subjects. Review and approval by the RDRC follows the same procedures as those delineated for review and approval by the IRB.

The RDRC reviews the protocol application for the following:

a) Is the pharmacological dose within allowable limits?

b) Were pharmacological dose calculations based on data available from published literature or other valid studies?

c) Is the radiation dose within allowable limits as defined in CFR 361.1?

d) Is the radiation exposure justified by the quality of the study being undertaken and the importance of the information it seeks to obtain?

e) Is each investigator qualified by training and experience to conduct the proposed research studies?

f) Is the investigator's or institution's license to handle radioactive materials appropriate?

g) Is the use of human subjects appropriate and does it meet applicable requirements?

h) Does the radioactive drug meet appropriate chemical, pharmaceutical, radiochemical and radionuclide standards of identity, strength, quality and purity?

i) Is the research design appropriate?

j) Are the packaging, label and labeling of the radioactive drug in compliance with all applicable regulations?

Submission to the RDRC uses the IRB Protocol form (IRB Form 001) and must include the signatures of Principal Investigator, Responsible Physician and the Department Chairman of the Principal Investigator. RDRC approval should be obtained prior to IRB review.

6.6.5 Full Institutional Review Board/Initial Review Procedures:

The completed Initial Application Package is submitted by the Principal Investigator to the IRB Secretary. S/He reviews the Package for completeness (including IRB approvals from other institutions, if applicable) and accuracy, creates a Clinical Investigation Authorization Form, assigns a number to the protocol and consent form and forwards the various forms as described in the IRB manual.

6.6.6 Clinical Research Associate Review:

The CRA will review the structure of the Investigator Files, the Case Report Forms and the protocol specific Subject Records to ensure that they meet all aspects of the protocol. This will include review to ensure that the protocol is in compliance with all BNL and federal regulations and that the protocol specific forms are in agreement with the description in the protocol. The main function of the CRA is to provide technical and regulatory information and support to the Principal Investigator.

6.7 Modification/Addendum to a Protocol:

A Principal Investigator must obtain, prior to implementation, IRB approval for any protocol amendment which significantly affects the safety of subjects, the scope of the investigation or the scientific quality of the study. Such a change may be requested by a Principal Investigator for any reason including an unanticipated reaction of a subject to a research procedure. Any significant unanticipated event must be reported to the IRB by the Principal Investigator immediately. No change in protocols can be initiated until the IRB has approved the change.

6.8 Recertification Review:

Schedules for Recertification Reviews are determined by the IRB at the time of the Initial and/or Modification/Addendum Review. The period for which the protocol has been approved is noted on the Decision Memo and is sent to the Principal Investigator as a condition of the protocol. The certification period is determined by the IRB during a Full Board Review and is based on factors such as the type of subjects involved, including disease state and/or vulnerability, previously reported adverse events and investigator/group experience with the proposed work.

It is IRB policy that a protocol which has reported no subjects for two consecutive years will be terminated and the PI will be informed he/she must submit a new application if they wish to continue the studies in the future.

7.0 PROTOCOL IMPLEMENTATION:

The BNL Clinical Research Center (CRC) shall only support research projects involving human subjects which have been approved by the BNL Institutional Review Board (IRB).

The ORA shall promulgate, at least monthly, a current listing of all IRB approved protocols. This listing shall be used by the CRC to determine whether research can be conducted.

Prior to commencement of research under an IRB-approved protocol, the P.I. shall perform the following:

7.1 Implementation of a New Protocol:

Upon notification that the IRB has approved a protocol, the Principal Investigator shall:

1. In consultation with the Responsible Physician, determine the format of the Subject Record, including preparation protocol-specific forms to be utilized in the Subject record.
2. Set up an Investigator file containing specific information as listed below.
3. Prepare the Case Report Form templates to be used during the study
4. Insure that all staff assigned to carry out the protocol are familiar with and have access to all pertinent documents associated with the study.
5. Obtain certification from the Clinical Research Associate (CRA) that the protocol specific Subject Record format and the Case Report Forms are appropriate and complete to insure that the study is conducted and documented in accordance with the protocol and the applicable regulations.

This certification shall be evidenced by a signed memorandum from the CRC Manager which states that the applicable documents have been reviewed and concurs with the Subject Records format and Case Report Forms prepared. This memo will be sent by the CRC Manager to the PI with a copy to the CRC Secretary. A copy of this memo should be retained in the Investigator Files. **This memo will constitute permission to start research.**

7.2 Implementation of a Protocol Amendment:

Upon notification that the IRB has approved an amendment to an existing protocol, the PI shall:

1. Update the Investigator File.
2. In consultation with the Responsible Physician, revise, as necessary, the format of the Subject Record, including preparation protocol-specific forms to be utilized in the Subject record.
3. Revise the Case Report Forms, as required to reflect the amended protocol procedures.
4. Insure that all staff assigned to carry out the protocol are aware of the amendment.
5. If any changes to the Subject record format and/or Case Report Forms were required, the PI must obtain a new certification from the Clinical Research Associate that all Subject Record formats

and Case Report Forms are appropriate and complete to insure that the study is conducted and documented in accordance with the revised protocol and the applicable regulations.

7.3 Subject Records:
The subject record shall document all elements of care provided to the subject during the course of the research study. The exact contents of the Subject Records will be protocol specific, but should contain the following. All subject records shall be controlled by the CRC.

It is the responsibility of the PI to insure that all subject records are accurate and complete.

7.3.1 Required Elements of a Subject Record:
Each subject record should contain the following:

Section 1
- Subject Information Form
- Radioisotope Summary/ Internal or External
- Inclusion Exclusion Criteria

Section 2
- Medical History and Physical
- Mental Exam
- Progress Notes
- Informed Consent form
- Laboratory Requests and STAT Reports
- Volunteer Fee Payment receipt form
- Subject Information Checklist
- Standing Orders

Section 3
- Subject Questionnaire Form

Section 4
- IRB Protocol Specific Forms

Section 5
- Follow-up Form
- Prescriptions

The subject records should be handled in accordance with CRC Policy.

7.4 Investigator File Requirements:
An Investigator File must be prepared and maintained by the PI for each IRB approved protocol. The Investigator File must be initiated prior to the start of the study. The exact contents of this file will be protocol specific but should contain:
Section 1

Full Protocol
IRB Protocol Summary
Unsigned consent form(s)
All IRB correspondence
IRB approval memo
Annual recertification
Amendments and Addendums
Collaborating Institution Protocol, consent forms, and Approval (if applicable).
Signature List

Section 2

Completed Form 1572 (only for protocols which have an IND)
IND or IDE Correspondence (if applicable for protocol)
Biosketches (NIH format or other) of PI, responsible physician and participating physicians)
Staff credential documentation

Section 3

Laboratory Certification for any tests (including the Brookhaven Occupational Medicine Clinic Laboratory certification).
Normal Laboratory Values: (This refers to the normal ranges which are printed out on the lab report; a copy of a typical laboratory with normal values should suffice).

Section 4

Product Information Sheets where a drug is being given as part of the protocol
Drug accountability receipt and disposition records and correspondence:
Investigator Brochure where applicable.
Certificate of analysis for drugs which are not FDA approved (if required)

Section 5

Case Report Form (CRF): (Blank copy of the checklist).
Grant or FWP application: (Can be in another file but must be accessible; the Face page & abstract should be in the Investigator file).
Location of Research Records: (a statement of where records and data reside is sufficient)
Subject ID code list (or where in the CRC the list resides)
Subject screening log (or a note as to where the log is kept)
Certificate of Confidentiality (if required by protocol)

Section 6

Subject accrual log.
Signed Consent Forms (or a note indicating the forms are in the Subject Record)
Adverse Event reports: (signed copies of report)
Correspondences with funding agency and FDA (if IND study) regarding serious adverse events
Correspondences with the CRC and other BNL organizations relative to the study
CRC Approval memo
Termination Form

7.5 Case Report Forms:

Case Report Forms (CRF) are considered to be essential documents and must be included in the Investigator's study file. CRFs may be printed or electronic documents.

In order to capture data, as required by the protocol, a case report form (CRF) will be produced for each subject entered into each research protocol. The data required by the protocol should be reported accurately in the CRF and should be consistent with the source documents (or discrepancies explained). Any change or correction should be dated, initialed and explained.

Any adverse events, concomitant medications and intercurrent illnesses should be reported in the CRFs in accordance with the protocol. Tests or examinations that are not conducted should be clearly reported. Any missed appointments, dropouts or withdrawals should be clearly reported and explained.

A template CRF checklist is provided as Appendix D. The Case Report Forms shall be maintained by the PI for in accordance with the above policies.

Contents of the Case Report Form will be protocol specific, but should contain the following:
Study Flow Sheet
Inclusion/Exclusion Criteria
Medical History and Physical
Radioisotope Summary (if applicable)
Mini mental Exams (if applicable)
Lab Reports
Rating Scales
Study Outcome
Adverse Events
Drug Accountability
Other protocol specific documentation

8.0 GUIDANCE IN THE CONDUCT OF CLINICAL RESEARCH:

8.1 Subject Recruitment

Refer also to FDA IRB Information Sheet "Advertising for Study Subjects"

In order to recruit volunteers for a study there is often a need to solicit subjects by using advertising, fliers or written material.

In order to insure that there is no misleading information given out, any media advertising, fliers or written material presented to the public for the purpose of recruitment must be reviewed and approved by the IRB prior to its use.

The language used must be appropriate to the study and is not to be considered as coercive.

The advertisement should not state or imply any direct benefit to the volunteer (other than fee paid).

A detailed process of how subjects are recruited (how, when and by whom) must be included in the protocol.

Subject reimbursement must be reasonable in relation to risks, discomfort or inconvenience to the subjects and not so large as to be perceived as coercive. Reimbursement is limited to the terms established in the approved IRB protocol. There can be no deviations from this procedure.

Staff supervised by the P.I. are not eligible to participate in the study.

8.2 Procedure for Enlisting a Subject in a Protocol:

1. The Principal Investigator, or his/her delegate, shall notify the CRC Receptionist when a subject has been identified for participation in a research study. Such notification should occur, at minimum, one day before commencement of the study. The PI shall provide the CRC Secretary with:
   - the participant's name,
   - birth date,
   - protocol number under which the research will be conducted.
   - name of the participating or responsible physician for the study.
2. The CRC Secretary, upon receipt of such notification, shall determine whether the individual has previously been involved with CRC research by reviewing the CRC Patient Card file.
3. If it is determined that the individual is a new subject, the CRC Secretary shall issue the individual a CRC Identification Number and create a Subject Record.
4. If it is determined that the individual has previously participated in clinical research, the existing Subject Record will be accessed.
5. The Subject Record format associated with the planned study will be assembled by the CRC Secretary and inserted in the Subject Record.

8.3 Confidentiality:

It is the PI's responsibility to protect the privacy of subjects and maintain confidentiality of data. To the extent reasonably possible, all references to the subject should be made by I.D. number rather than by name.

When research involving use of illegal or sensitive substances is performed, obtaining a Certificate of Confidentiality from NIH is recommended. Federal Law referred to as the Public Health Service Act Section 301(d) provides Federal protection of confidentiality when the data collected is deemed "sensitive". Further information can be found in the CRC policy Manual section 4.4.

8.4 Informed Consent Process:

All consent must be documented on the IRB-approved Consent Form associated with the protocol being conducted. Each new protocol needs a separate consent form.

A process for obtaining informed consent which enhances independent and thoughtful decision making, including who will obtain informed consent and where the process will take place, is a required element of the protocol application.

The subject must have the capacity to provide informed consent. That capacity shall be documented in the subject record.

Consent must be obtained, in writing, prior to conduct of any aspect of the protocol .

Consent may only be obtained by personnel who are listed on the protocol and have been credentialed by the CRC to obtain informed consent. There can be no changes or amendments to the Informed Consent document unless pre-approved by the IRB.

For studies lasting several months, consideration should be given to repeating the consenting process upon the return of the subject or verifying that the subject still understands the nature of the protocol.

8.5 Inclusion/Exclusion:

The fundamental guiding principles in ethical human subject research are respect for persons, beneficence, and justice. To conduct research in line with these principles, it is the principal investigator's obligation to design a study that reduces risk, increases benefit, and assures equitable selection of participants. This is achieved by using procedures that are consistent with sound research design. Sound research design dictates that subjects at increased risk due to the nature of the research be identified and excluded from participation. Furthermore, subject selection must be limited to a group with well defined characteristics so that data collected will be meaningful. To reduce risk and increase benefit research involving human subjects must have specific criteria of inclusion and exclusion.

To document that the protocol-specific inclusion/exclusion criteria have been considered and adhered to, the P.I. shall create an Inclusion/Exclusion Criteria checklist as part of the Subject Record/CRF template package assembled prior to commencement of a clinical protocol. The criteria elements of this form shall mirror the criteria established by the P.I. in the IRB-approved protocol.

8.6 Completion and filing of Study Documents:

8.6.1 Completion of Subject Record:

1. It is the responsibility of the Principal Investigator to insure that all subject records are returned to the CRC Main Desk following completion of the research study. This responsibility may be delegated. The Subject Record shall be returned to the CRC no later than five (5) working days after the completion of the research study.

2. Upon return of the Subject Record to the CRC Main Desk, the CRC Secretary shall determine that it is complete and tag it for review by the Subject Records Reviewer.

3. The CRC Secretary shall inform the CRC Manager of incidents when Subject Records are not returned in a timely manner. Failure to return subject records in a timely manner may result in delay of enrollment of additional subjects.

8.6.2 Maintenance of Investigator Files:

It is the responsibility of the Principal Investigator to ensure that the Investigator Files are kept current and in accordance with the guidelines set forth here. The CRA may assist the PI in maintenance of these records.

8.6.3 Maintenance of Case Report Forms:

It is the responsibility of the Principal Investigator to ensure that the Case Report Forms are kept current and in accordance with the guidelines set forth here. The CRA may assist the PI in maintenance of these records.

8.7 Drug Accountability

Controlled substances are highly regulated compounds. Brookhaven Science Associates holds the only Drug Enforcement License (DEA) that allows for controlled substances to be used in research at BNL. BSA must assure that employees that handle controlled substances (i.e. those substances defined in 21 CFR 1300 - end) do so in a safe manner that is in compliance with Federal and State regulations. Failure to comply with regulations in any program at any level puts BSA's DEA license in jeopardy. Loss of this license would have devastating effects on major biomedical research programs on-site.

Appropriate measures shall be applied when procuring, transporting, storing, using, and disposing of controlled substances. The Central Pharmacy is the control point and has responsibility for BSA controlled substances used for research at BNL. The Central Pharmacy operates under the direction of the Pharmacist and the Clinical Research Center (CRC). The policy can be found in the CRC policy manual section 8.1 through 8.3 and the procedures for controlled substances and pharmaceuticals can be found in Attachment A of CRC Policy Manual section 8.1.

8.8 Adverse Event Reporting

HHS regulation – 45 CFR 46.103 (b) (5) – requires that an institution's Multiple Project Assurance contain written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and appropriate federal officials of any unanticipated problems involving risks to subjects or others. FDA regulations covering clinical research performed under an IND-21 CFR 312.32

requires that the Investigator/Sponsor notify FDA in a written IND Safety Report of any adverse experience associated with the use of the drug covered by the IND that is both serious and unexpected.

An adverse event is considered serious if it is:

Fatal, life-threatening, requires hospitalization, prolongs hospitalization, persistent or significant disability, causes birth defects or may require medical or surgical intervention to prevent one of the outcomes listed above.

The definitions and BNL reporting policy can be found in section 4.6 of the CRC policy Manual.

8.9 Subject Accrual

Subject Accrual Plan:

1. All initial subject information will be entered at CRC.

2. All subjects should be admitted in initial visit through CRC where a note will be made as to which protocol they are enrolling and if there are any other protocols in which they are, or have been, enrolled.

3. A note will be made in the file when the subject has signed the study consent. This will constitute enrollment.

4. Facility specific information entered at facility; protocol specific documents will be generated and included in the appropriate files.

5. An advisory should be sent to the PI when the number of subjects/protocol is at 80% of the total number of subjects authorized for the protocol and again at 100% of the maximum accrual.

6. Credentialing information will be incorporated in the investigator records.
7. A note will be made in the file if the subjects either completes the study or withdraws from the study.

8. The number of subjects should be reconciled by the PI and the CRA on a periodic basis. A memo should be written on at least an annual basis attesting that the number of subjects is reconciled. A copy of this memo should be submitted to the IRB as part of the annual recertification process.

8.10 Subject Follow Up Procedures:

A follow-up plan is a required element of the protocol application. This follow up should assist in determining the welfare of the subject, but may also be used to inform the subject of the findings of the study, if appropriate and applicable.

The follow-up plan contained in the IRB-approved protocol must be followed and documented in the Subject Record.

Follow-up procedures may only be performed by personnel who have been deemed competent to perform such follow-up by the CRC Credentialing Committee and who have been identified by the P.I. in the protocol application, or subsequent addendum.

8.11 FDA Annual Reporting:

A sponsor (or sponsor-investigator) shall within 60 days of the anniversary date that the IND went into effect, submit a brief report of the progress of the investigation that includes:

(a) Individual study information. A brief summary of the status of each study in progress and each study completed during the previous year. The summary is required to include the following information for each study:

(1) The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed.

(2) The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.

(3) If the study has been completed, or if interim results are known, a brief description of any available study results.

(b) Summary information. Information obtained during the previous year's clinical and non clinical investigations, including:

(1) A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.

(2) A summary of all IND safety reports submitted during the past year.

(3) A list of subjects who died during participation in the investigation, with the cause of death for each subject.

(4) A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.

(5) A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trails, and information about bioavailability.

(6) A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.

(7) A summary of any significant manufacturing or microbiological changes made during the past year.

(c) A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigational plan shall contain the information required under Sec. 312.23(a)(3)(iv).

(d) If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.

(e) A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.

(f) A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.

(g) If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting.

8.12 Annual reports for protocols involving RDRC approval

For protocols which have RDRC approval, a report must be filed every January with the Chair of the RDRC committee. The following information must be supplied for each protocol which was active during any part of the preceding year:

1. The age of each subject
2. The sex of each subject
3. The amount and chemical form of each administration of radioactivity to each subject
4. The total number of subjects enrolled during the year
5. The total number of subjects approved for this protocol
6. If any of the subjects participated in any other protocol involving the administration of radioactivity
7. The number of subjects under 18

This information must be supplied to the RDRC Chair prior to the 15th of January. This information will be sent to the FDA in an annual report.

Principal Investigator Manual

Appendix A - Belmont Report

Principal Investigator Manual

Belmont Report
The Belmont Report Office of the Secretary Ethical Principles and Guidelines for the Protection of Human Subjects of Research The National Commission for the Protection of Human Subjects of Biomedical and Behavioral ResearchApril 18, 1979

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human subjects for participation in such research and **(iv)** the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

Principal Investigator Manual

National Commission for the Protection of Human Subjectsof Biomedical and Behavioral Research

Members of the Commission

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.

Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.

Robert E. Cooke, M.D., President, Medical College of Pennsylvania.

Dorothy I. Height, President, National Council of Negro Women, Inc.

Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.

Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.

Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion.

*** *David W. Louisell, J.D., Professor of Law, University of California at Berkeley.*

Donald W. Seldin, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas at Dallas.

****Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.*

*** *Robert H. Turtle, LL.B., Attorney, VomBaur, Coburn, Simmons & Turtle, Washington, D.C.*

*** *Deceased.*

Table of Contents

Principal Investigator Manual

3. Justice

C. Applications

1. Informed Consent

2. Assessment of Risk and Benefits

3. Selection of Subjects

Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes(1) intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

Part A: Boundaries Between Practice & Research

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when "research" are not carefully defined.

Principal Investigator Manual

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.(2) By contrast, the term "research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.(3)

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

Part B: Basic Ethical Principles

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respect for Persons. -- Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those

considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. -- Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: **(1)** do not harm and **(2)** maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case

of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. -- Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are **(1)** to each person an equal share, **(2)** to each person according to individual need, **(3)** to each person according to individual effort, **(4)** to each person according to societal contribution, and **(5)** to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably

effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

Part C: Applications

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. -- Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject,

being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that **(1)** incomplete disclosure is truly necessary to accomplish the goals of the research, **(2)** there are no undisclosed risks to subjects that are more than minimal, and **(3)** there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be

able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitle.

2. Assessment of Risks and Benefits. -- The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Principal Investigator Manual

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: **(i)** Brutal or inhumane treatment of human subjects is never morally justified. **(ii)** Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. **(iii)** When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation). **(iv)** When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. **(v)** Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. -- Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the

principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

(1) Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have

also been adopted, the best known being that of the American Psychological Association, published in 1973.

(2) Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

(3) Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

National Institutes of Health

Bethesda, Maryland 20892

Principal Investigator Manual

Appendix B - Example of Medical Records

Principal Investigator Manual

Appendix C - Example of Investigator Files

Principal Investigator Manual

Investigator Checklist

Section 1

- ☐ Full Protocol
- ☐ IRB Protocol summary
- ☐ Unsigned consent form(s)
- ☐ All IRB correspondence
- ☐ IRB approval memo
- ☐ Annual recertification
- ☐ Amendments and Addendums
- ☐ Collaborating Institution Protocol, consent forms, and Approval (if applicable).
- ☐ Signature List

Section 2

- ☐ Completed Form 1572 (only for protocols which have an IND)
- ☐ IND or IDE Correspondence as related to protocol
- ☐ Biosketches (NIH format or other) of PI, responsible physician and participating physicians)
- ☐ Staff credential documentation and licenses

Section 3

- ☐ Laboratory Certification for any tests (including the Brookhaven Occupational Medicine Clinic Laboratory certification).
- ☐ Normal Laboratory Values: (This refers to the normal ranges which are printed out on the lab report; a copy of a typical laboratory with normal values should suffice).

Section 4

- ☐ Investigator Brochure or Product Information Sheets where a drug is being given as part of the protocol
- ☐ Drug receipt and disposition records and correspondence:

Section 5

- ☐ Case Report Form (CRF): (Blank copy of the checklist).
- ☐ Grant or FWP application: (Can be in another file but must be accessible; the Face page & abstract should be in the Investigator file).
- ☐ Location of Research Records: (a statement of where records and data reside is sufficient)
- ☐ Certificate of analysis for drugs which are not FDA approved
- ☐ Subject ID code list (or where in the CRC the list resides)
- ☐ Subject screening log (memo indicating where the log is kept)
- ☐ Certificate of Confidentiality (if required)

Section 6

- ☐ Subject accrual log.
- ☐ Signed Consent Forms (memo to indicate the forms are in the Medical Records)
- ☐ Adverse Event reports: (signed copies of report)
- ☐ Correspondences with funding agency and FDA (if IND study) regarding serious adverse events
- ☐ Correspondences with the CRC and other BNL organizations relative to the study
- ☐ Termination form

Preparer _____ Date_____

CRA: _____ Date_____

Principal Investigator Manual

Appendix D - Example of Case Report Form Checklist

Brookhaven National Laboratory

Clinical Research Center Subject No: _____

IRB No._____ Subject Initials: _____

Brookhaven National Laboratory
Clinical Research Center
Upton, New York 11973

CASE REPORT FORM

IRB Title: _____

Project (IRB) No.: ____

Principal Investigator: _____

Responsible Physician: _____

I have reviewed all the data in the case report forms and found them to be complete and accurate.

_____ _____

Principal Investigator's Signature Date

(To be signed and dated after the subject has ended participation in the study)

Brookhaven National Laboratory

Clinical Research Center Subject No: _____

IRB No._____ Subject Initials: _____

GENERAL INSTRUCTIONS

1. Use black ballpoint ink to record data on these forms.

2. Record the patient's initials (order: first, middle, last) and patient number on the top of each page in the spaces provided. If the patient has no middle initial, please enter a dash (-) or an "X."

3. To make corrections, draw a single line through the error, then record the correct response and initial and date the correction. DO NOT ERASE, OBLITERATE, OR WHITE-OUT ANY ERRORS. Do not make corrections by writing over an erroneous entry.

4. The principal investigator must sign and date the cover page of this case report form after the patient has ended participation in the study.

Brookhaven National Laboratory

Clinical Research Center Subject No: _____

IRB No._____ Subject Initials: _____

MONITORING VISIT LOG

Principal Investigator: _____

DATE	CRA	STUDY CONTACT PERSON

Brookhaven National Laboratory

Clinical Research Center Subject No: _____

_____

IRB No._____ Subject Initials: _____

_____

Visit Date: _____

DEMOGRAPHICS AND PHYSICAL INFORMATION

DEMOGRAPHICS

Date of Birth ___/___/___ (M D Y) Sex ___ M ___ F Race: ___ Caucasian ___ Oriental/Asian ___ Black ___ Hispanic ___ Native American ___ Other _____ (specify)	If the patient is female, she is: ___ Surgically Sterile _____ (specify) ___ Post-Menopausal ___ Premenarcheal ___ Using a protocol approved method of birth control for 3 months prior to start of study _____ (specify)

VITAL SIGNS

Height:	Weight:	Temperature:	Pulse:	Respiration's:	Blood Pressure:
inches	Lbs	°F	bpm	/min	/ mmHg

Brookhaven National Laboratory

Clinical Research Center Subject No: _____

IRB No._____ Subject Initials: _____

Visit Date: _____

SUBJECT ELIGIBILITY CHECKLIST

INCLUSION/EXCLUSION CRITERIA FORM
(COCAINE ABUSER GROUP)

INCLUSION CRITERIA:		Yes	No	N/A
1.	Ability to understand and give informed consent	☐	☐	☐
2.	20-55 years of age	☐	☐	☐
3.	DSM IV diagnosis for active cocaine dependence	☐	☐	☐
4.	At least a 6 month history of cocaine abuse (at least 3.5 grams/week)	☐	☐	☐
5.	Use of cocaine by smoked or iv route	☐	☐	☐
6.	In an inpatient or outpatient detoxification program	☐	☐	☐
EXCLUSION CRITERIA:				
7.	Pregnant	☐	☐	☐
8.	Present or past history of neurological or psychiatric disease apart from cocaine abuse.	☐	☐	☐
9.	Current medical illness	☐	☐	☐
10.	History of cardiovascular or endocrinological disease	☐	☐	☐

Brookhaven National Laboratory

Clinical Research Center Subject No: _____

_____

IRB No._____ Subject Initials: _____

_____

Visit Date: _____

SUBJECT ELIGIBILITY CHECKLIST

INCLUSION/EXCLUSION CRITERIA FORM
(*NORMAL SUBJECTS)*

INCLUSION CRITERIA:		Yes	No	N/A
1	Ability to understand and give informed consent	☐	☐	☐
	2. 20-55 years of age	☐	☐	☐

EXCLUSION CRITERIA: criteria should follow from protocol (Section I) and specify the following:

3. pregnant			
4. present or past history of neurological or psychiatric disease	☐	☐	☐
5. alcohol or substance abuse (except for caffeine or nicotine)	☐	☐	☐
6. Subject with a history of drug addiction in one first degree relative or 2 or more second degree relatives	☐	☐	☐
7. History or cardiovascular or endocrinological disease	☐	☐	☐
8. Head trauma with loss of consciousness	☐	☐	☐
9. Medical illness which may affect brain function	☐	☐	☐

Brookhaven National Laboratory

Clinical Research Center Subject No: _____

IRB No._____ Subject Initials: _____

Visit Date:_____

STUDY PRESCREENING

		Yes	No	NA
1	Lab screening consent form signed:	☐	☐	☐
2	Were urine tests for psychoactive drug use ordered?	☐	☐	☐
3.	Was pregnancy test administered?	☐	☐	☐
4.	Complete history and physical exam completed	☐	☐	☐
5.	Was EKG performed (no cardiac abnormalities)	☐	☐	☐
1	Subject meets Eligibility Criteria	☐	☐	☐

Brookhaven National Laboratory

Clinical Research Center Subject No: _____

IRB No._____ Subject Initials: _____

Visit Date:_____

Test and PROCEDURES – DAY 1, VISIT 1

	Yes	No	NA
5. Lab Consent Form administered			
6. Study Consent Form administered			
7. Urine toxicology test negative			
4. Pregnancy test negative			
5. Multi-Dimensional Personality Inventory completed			
6. Drug history form completed (*all subjects*)			
7. PET subject information form completed			
8. tobacco questionaire administered			

Cocaine abusers only:

9. Cocaine Selective Withdrawal Assessment completed
10. BPRS form completed
11. Drug evaluation form completed

Procedure:

12. cardiac monitoring during study _____ **(Time)**
13. 3 cc saline via IV administered _____ **(Time)**
14. Subject receives F-18 FDG/PET scan: _____ **(Time)**
15. Mood scales administered _____ **(Time)**
16. Sedative rating scales administered _____ **(Time)**

Date	Run Number	Tracer	Dose	Time

17. Doctor motor evaluation _____ **(Time)**
18. Imaging run data sheet completed _____ **(Time)**
19. Blood sampling completed _____ **(Time)**

REMINDER: DETAILS OF ALL ADVERSE EVENTS MUST BE SOLICITED AND RECORDED AT EACH VISIT.

Brookhaven National Laboratory

Clinical Research Center Subject No: _____

IRB No._____ Subject Initials: _____

Visit Date:_____

STUDY PROCEDURES DAY 2, VISIT 2

Screening:	**Yes**	**No**	**NA**
1. Urine toxicology test negative?			
2. Pregnancy test negative			
3. Brief physical exam completed			

Procedure:

4. cardiac monitoring during study _____ **(Time)**
5. Ativan administered (30 microg/kg iv) _____ **(Time)**
6. Blood sample for Ativan analysis _____ **(Time)**
7. Subject receives F-18 FDG/PET scan: _____ **(Time)**
8. Mood scales administered _____ **(Time)**
9. Sedative rating scales administered _____ **(Time)**

Date	Run Number	Tracer	Dose	Time

10. Doctor motor evaluation _____ **(Time)**
11. Imaging run data sheet completed _____**(Time)**
12. Blood sampling completed _____ **(Time)**
13. Follow-up call by: (next working day) _____ Date_____

Comments:

_____

_____

_____

_____

_____

REMINDER: DETAILS OF ALL ADVERSE EVENTS MUST BE SOLICITED AND RECORDED AT EACH VISIT AND FOLLOW-UP.

Brookhaven National Laboratory

Clinical Research Center Subject No: _____

IRB No._____ Subject Initials: _____

Visit Date:_____

STUDY SCREENING / PROCEDURES, VISIT 3 (2 – 6 weeks after visit 2)

Cocaine Abusers Only

Screening:

	Yes	**No**	**NA**
1. Urine toxicology negative			
2. Pregnancy test negative			
3. Study Consent Form administered			
4. Brief physical exam completed			
5. PET subject information completed			
6. Subject meets Eligibility Criteria			

Procedure:

7. cardiac monitoring during study _____ **(Time)**
8. 3 cc saline via IV administered _____ **(Time)**
9. Subject receives F-18 FDG/PET scan: _____ **(Time)**
10. Mood scales administered _____ **(Time)**
11. Sedative rating scales administered _____ **(Time)**

Date	Run Number	Tracer	Dose	Time

12. Doctor motor evaluation _____ **(Time)**
13. Imaging run data sheet completed _____ **(Time)**
14. Blood sampling completed _____ **(Time)**

REMINDER: DETAILS OF ALL ADVERSE EVENTS MUST BE SOLICITED AND RECORDED AT EACH VISIT AND FOLLOW-UP.

Brookhaven National Laboratory

Clinical Research Center Subject No: _____

IRB No._____ Subject Initials: _____

Visit Date:_____

STUDY SCREENING / PROCEDURES, VISIT 4

Cocaine Abusers Only

Screening:	**Yes**	**No**	**NA**
1. Urine toxicology test negative			
2. Pregnancy test negative			
3. Brief physical exam completed			

Procedure:

4. cardiac monitoring during study _____ **(Time)**
5. Ativan administered (30 microg/kg iv) _____ **(Time)**
6. Blood sample for Ativan analysis _____ **(Time)**
7. Subject receives F-18 FDG/PET scan: _____ **(Time)**
8. Mood scales administered _____ **(Time)**
9. Sedative rating scales administered _____ **(Time)**

Date	Run Number	Tracer	Dose	Time

10. Doctor motor evaluation _____ **(Time)**
11. Imaging run data sheet completed _____ **(Time)**
12. Blood sampling completed _____ **(Time)**
13. Follow-up call by: (next working day) _____ Date_____

Comments:

_____

_____

_____

_____

_____

REMINDER: DETAILS OF ALL ADVERSE EVENTS MUST BE SOLICITED AND RECORDED AT EACH VISIT AND FOLLOW-UP.